

A regio- and stereoselectivity and molecular mechanism study on the addition reactions of morpholine and m-CPBA to 9 α -hydroxyparthenolide using DFT calculations

Sana El Hamidi ¹, Wafaa Boumya ¹, Redouan Hammal ², Mohamed Moumou ², Asmaa Ben Naji ¹, M'hamed Sadiq ¹, Ahmed Chekroun ², Ahmed Benharref ², Noureddine Barka ^{1,*} and Mohamed Abdennouri ¹

¹ Sultan Moulay Slimane University of Beni-Mellal, Research Group in Environmental Sciences and Applied Materials (SEMA), FP Khouribga, B.P. 145, 25000 Khouribga, Morocco

² Cadi Ayyad University, Faculty of Sciences Semlalia, Laboratory of Biomolecular Chemistry Natural Substances and Reactivity (URAC 16), BP 2390, Marrakech, Morocco

Abstract: The chemoselectivity and stereospecificity of the addition of the morpholine and the meta-chloroperoxybenzoic acid (m-CPBA) onto 9 α -hydroxyparthenolide were studied using Density Functional Theory (DFT) calculations with the B3LYP/6-311+G(d,p) computational level within the Molecular Electron Density Theory (MEDT), to demonstrate the key role of the Global Electron Density Transfer (GEDT) and to examine the polar character of these reactions. This work is divided into two parts; the first part concerns the reaction between the morpholine and the 9 α -hydroxyparthenolide. The second part deals with the epoxidation of the 9 α -hydroxyparthenolide by m-CPBA followed by the addition of the morpholine to the major product resulting from the epoxidation step. The obtained results show that the reaction between the morpholine and the 9 α -hydroxyparthenolide takes place on the double bond C₃=C₄. On the other hand, when 9 α -hydroxyparthenolide is attacked by m-CPBA, the epoxidation reaction is carried out on the double bond C₁=C₂.

Keywords: 9 α -Hydroxyparthenolide; Epoxidation; DFT; GEDT; Polar reactions.

1. Introduction

The regio and stereoselectivity in organic synthesis are crucial parameters, especially when the reaction product must be a particular regio- or stereoisomer, such as pharmaceutically active compounds. Therefore, it is interesting to understand the parameters that induce the different types of selectivity and thus be able to control them. To fully understand the chemical process of these reactions and provide valuable predictions to the experimenters, a theoretical study seems necessary.

It is important to point out that the study of the chemical reactivity of the compounds used in the manufacture of drugs has been the subject of enormous experiments carried out by researchers to find drugs effective against cancer, which remains one of the leading causes of death. Many chemotherapeutic agents have been developed to treat different types of cancer, but the use of these agents causes many undesirable effects. This underlines the urgent need to develop novel chemotherapeutic agents with higher bioactivity and

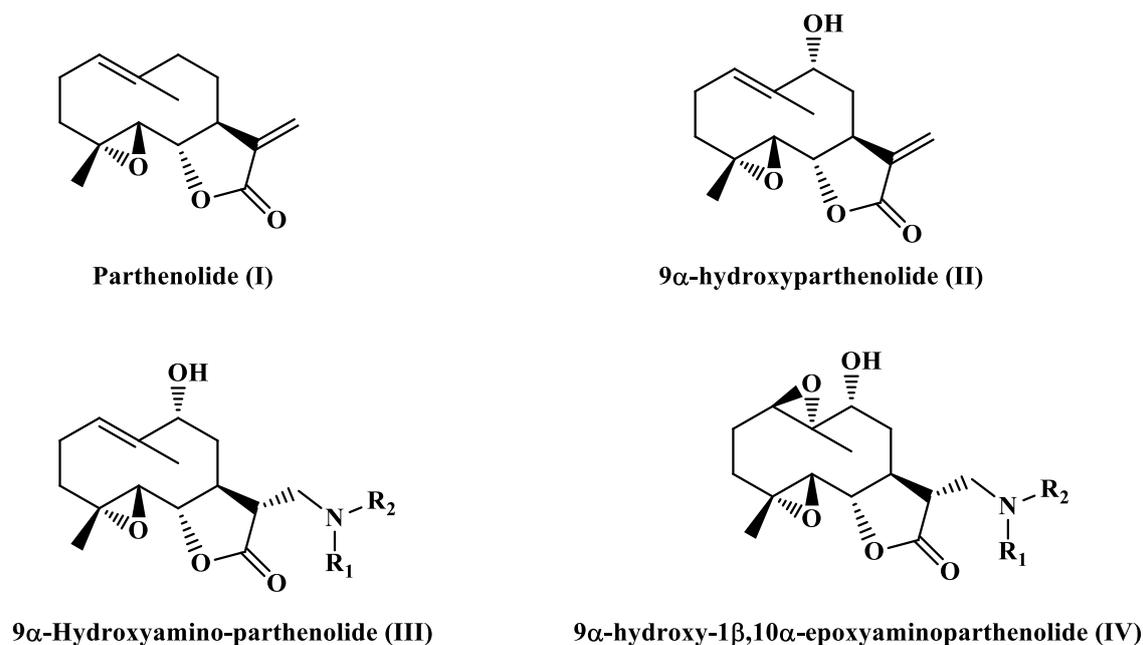
fewer side effects. One of the most promising approaches for obtaining novel therapeutic agents in medicinal chemistry is the functionalization of natural products.

In this context, the parthenolide (PTL), which is purified initially from the shoots of feverfew (*Tanacetum parthenium*), has shown potent anti-cancer and anti-inflammatory activities ¹. However, this compound is faintly soluble in water, which limited its potential therapeutic use in the human body. For this reason, the fixation of amine groups to the parthenolide is necessary to make it more soluble and more biologically active. Given the high biological activity of aminoparthenolides, series of their hydroxy and epoxy-analogs types II and III (Scheme 1) were synthesized.

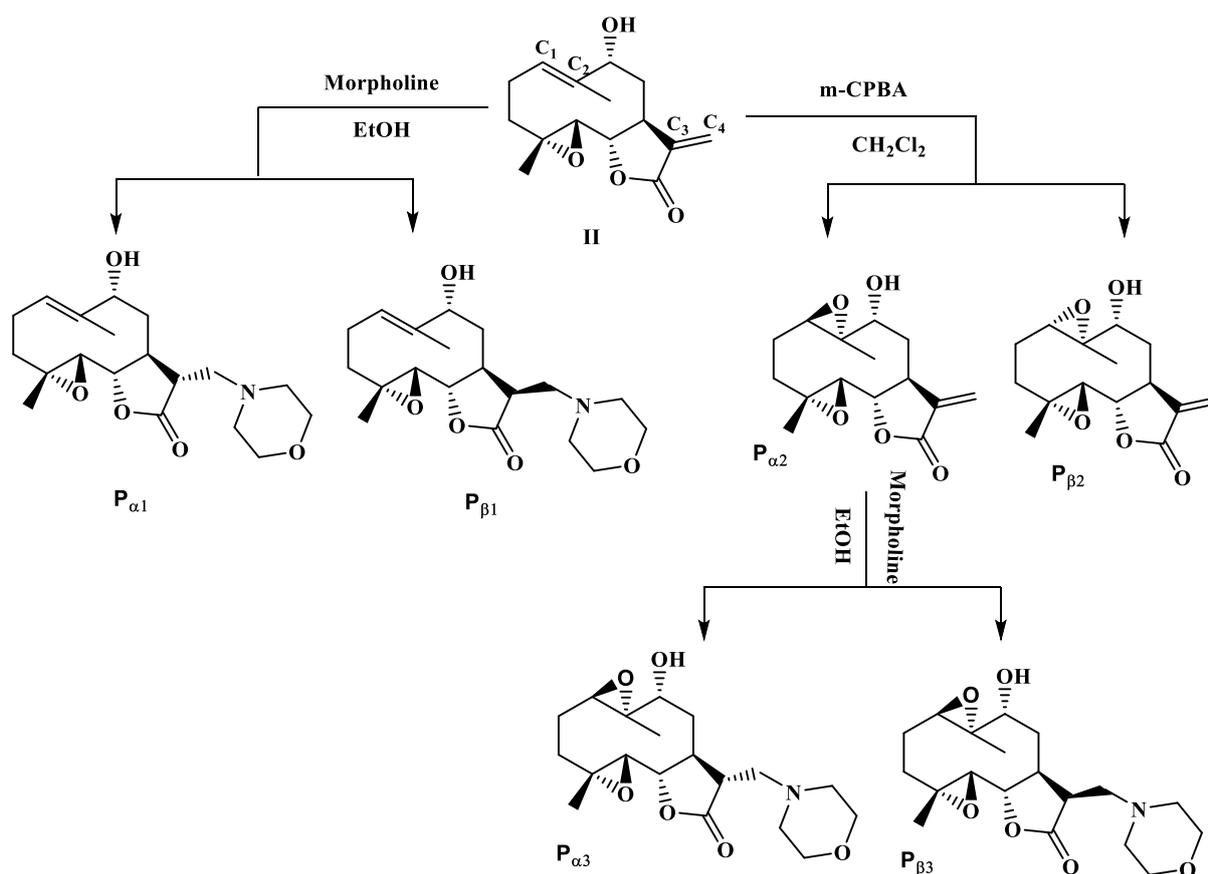
Generally, understanding the changes in molecules structure during a chemical reaction is not easy in many cases because these changes take place in a short time. For this reason, specific theories are important to examine and understand the molecular reactivity and to study the reaction mechanisms.

*Corresponding author: Noureddine Barka
Email address: barkanoureddine@yahoo.fr
DOI: <http://dx.doi.org/10.13171/mjc10502005221429nb>

Received April 3, 2020
Accepted April 18, 2020
Published May 22, 2020



Scheme 1. Structure of the parthenolide and its derivatives



Scheme 2. Addition of the morpholine and the m-CPBA onto the 9α-hydroxy parthenolide

With the increase in computing power of computers, the improvement of algorithms and the development of original approaches in the methods of numerical resolution of the equations of quantum mechanics have made it possible to obtain numerical parameters that can explain the results obtained in experiments. It is possible to access with very high precision all

the electronic properties of chemical systems and to calculate their variations along the reaction paths. In particular, quantum theories of reactivity currently make it possible not only to develop reaction mechanisms and energy profiles but also to justify and predict experimental chemo-, stereo- and regioselectivity.

In this study, we present theoretical justifications for the regio- and stereoselectivity experimentally observed² during the addition of morpholine to the 9 α -hydroxypartenolide in the first step. Then, the epoxidation of the 9 α -hydroxypartenolide by the m-CPBA followed by the addition of the morpholine according to the reaction sequences proposed in the (Scheme 2). Different theoretical approaches were used, such as the frontier molecular orbital theory (FMO), the calculation of activation energies, and the reactivity indices derived from DFT.

2. Theoretical and computational methods

2.1. Global and local reactivity indices

Organic reactions can be classified as non-polar or polar; it depends on the overall electronic character of the bond formation and/or bond-breaking along with the reaction. The electrophilic or nucleophilic power of a molecule is related to its ability to exchange electron density along with a reaction. The description of this power requires taking into consideration the electronic structure of the system, which could be possible only with a quantum description.

Furthermore, to solve the problem of the chemical reactivity of organic and pharmaceutical molecules and to explain why some sites of the molecules are more reactive than others, several theories have been established for the study of chemical reactivity. This is following the transition state theory (developed by Eyring in 1931)³, frontier molecular orbital theory (initiated by K. Fukui in 1952)⁴ and the density functional theory (proposed by G. Klopman in 1968)⁵.

With the application of the quantum or molecular mechanics, it is possible to obtain several parameters such as the structural parameters (bond lengths, valence angles, hydrogen bonds), the energy parameters (binding energy, enthalpy of formation), and the electronic parameters (charges, orbital energies (Highest Occupied Molecular Orbital (HOMO), Lowest Unoccupied Molecular Orbital (LUMO)), E_{gap} (energy difference between E_{HOMO} and E_{LUMO})...).

The calculated levels of energy of HOMO and LUMO can be used for the calculation of other parameters related to the stability of the molecule, such as ionization energy (I), electron affinity (A), electronegativity (χ), electronic chemical potential (μ), chemical hardness (η), chemical softness (S), and electrophilicity index (ω). These parameters can be calculated using the following equations:

$$\text{Ionization Energy (I)} = -E_{\text{HOMO}},$$

$$\text{Electron Affinity (A)} = -E_{\text{LUMO}},$$

$$\text{Electronegativity } (\chi) = -(E_{\text{HOMO}} + E_{\text{LUMO}})/2 \text{ }^6,$$

$$\text{Electronic Chemical Potential}$$

$$(\mu) = -(\chi) = (E_{\text{HOMO}} + E_{\text{LUMO}})/2 \text{ }^7,$$

$$\text{Chemical Hardness } (\eta) = (E_{\text{LUMO}} - E_{\text{HOMO}}) \text{ }^8,$$

$$\text{Electrophilicity Index } (\omega) = \mu^2/2\eta \text{ }^9 \text{ and}$$

$$\text{molecular softness (S)} = 1/2\eta \text{ }^{10}.$$

The nucleophilicity index N is referenced to the HOMO energy of tetracyanoethylene (TCE) as $N = E_{\text{HOMO}}(\text{Nu}) - E_{\text{HOMO}}(\text{TCE})$ ¹¹.

In a polar reaction, the breaking and formation of bonds take place at a specific site of a reactive molecule. If a molecule has several points with similar reactivity, we can talk of regio or chemoselectivity as in the case of cycloaddition reactions. In these reactions, the different approach modes of a reagent towards the other can yield two competitive regioisomers. The most favorable regioisomeric channel is that involving the bond formation between the most electrophilic and the most nucleophilic center of the reagents. Consequently, it is desirable to have local reactivity indices able to characterize these relevant centers and their position in organic molecules. The local electrophilicity index ω_k , the local nucleophilicity index N_k , the Parr functions (P_k^+ , P_k^-)¹² and the Fukui function (f_k^+ , f_k^-)¹³ have been confirmed to be useful tools in the study of the regioselectivity in cycloaddition reactions. The local electrophilicity and nucleophilicity indices were calculated as $\omega_k = \omega \cdot P_k^+$ and $N_k = N \cdot P_k^-$, respectively¹². The electrophilic P_k^+ and nucleophilic P_k^- Parr functions are obtained by the analysis of the Mullikan atomic spin density (ASD) of the radical anion and radical cation of the reactants. The Fukui functions (FF) are calculated using the procedure proposed by Yang and Mortier, based on a finite difference method: $f_k^+ = \rho_k(N+1) - \rho_k(N)$ (for nucleophilic attack), $f_k^- = \rho_k(N) - \rho_k(N-1)$ (for electrophilic attack) and $f_k^0 = \frac{\rho_k(N+1) - \rho_k(N-1)}{2}$ (for radical attack), where $\rho_k(N)$; $\rho_k(N-1)$ and $\rho_k(N+1)$ are the gross electronic populations of the site k in neutral, cationic, and anionic systems, respectively¹⁴.

2.2. Computational details

DFT calculations were carried out using the Becke three-parameter hybrid exchange functional and the Lee-Yang-Parr correlation functional (B3LYP)¹⁵ together with the standard 6-311+G(d,p) basis set¹⁶. Optimizations were carried out using the Bery analytical gradient optimization method¹⁷. Frequency calculations characterized the stationary points to verify that the transition state (TS) has one and only one imaginary frequency. The IRC was performed and plotted to confirm that the TS is well connected to both minima (reagents and products)¹⁸⁻²⁰.

The electronic structures of the stationary points and the bond orders (Wiberg indices) were analyzed using the natural bond orbital method (NBO)^{19,20}.

The values of enthalpies, entropies, and free energies were calculated using standard statistical thermodynamics. The Gaussian 09W suite of programs was used in all calculations ²¹.

3. Results and Discussion

3.1. Addition of morpholine and m-CPBA onto 9 α -hydroxyparthenolide

3.1.1. Analysis of the CDFT indices of the reagents

Several studies devoted to organic reactions have shown that the analysis of the reactivity indices defined within the conceptual density functional theory (CDFT) is a powerful tool to understand the reactivity in polar reactions. Global DFT reactivity indices, namely, the electronic chemical potential μ , chemical hardness η , softness S , electrophilicity ω , nucleophilicity N indices and the maximum number of electrons transferred ΔN_{\max} of reagents are given in Table 1.

This Table indicates that the electrophilic and nucleophilic character of 9 α -hydroxyparthenolide changes from one reaction to the other, depending on the attacking reagent. In the first reaction, the electronic chemical potential of morpholine, $\mu = -3.103$ eV, is higher than that of the 9 α -hydroxyparthenolide, $\mu = -4.239$ eV. This result indicates that the global electron density transfer (GEDT) will go from the morpholine towards the 9 α -hydroxyparthenolide. The morpholine presents an electrophilicity ω index of 0.755 eV and a nucleophilicity N index of 2.851 eV, being classified as strong nucleophile than the 9 α -hydroxyparthenolide, which has an electrophilicity ω index of 1.890 eV and a nucleophilicity N index of 2.524 eV. Consequently, the 9 α -hydroxyparthenolide behaves as an electrophile, while the morpholine behaves as a nucleophile.

In the reaction between 9 α -hydroxyparthenolide and m-CPBA, the electrophilicity ω index, the nucleophilicity N index, and the electronic chemical potential μ of the 9 α -hydroxyparthenolide were 1.878, 2.495 and -4.246 eV, respectively. While those corresponding to m-CPBA were 2.147, 1.779, and -4.748 eV, respectively, these results indicate that the 9 α -hydroxyparthenolide is a nucleophile, while, m-CPBA is an electrophile. The electrophilicity ω and nucleophilicity N values indicate that the epoxidation reaction will have a high polar character, in agreement with the high difference between their electronic chemical potentials μ .

On the other hand, the prediction of the electrophilic/nucleophilic character is also well confirmed by the frontier molecular orbital theory. So, the formation of the complex resulted in an exchange of electrons between the two-molecular orbital HOMO of the donor (nucleophile) and LUMO of the acceptor (electrophile). The reaction corresponding to the lowest difference of energy between the two orbital HOMO and LUMO is always favored. The energy gap in reaction (1) between HOMO of the morpholine and LUMO of the 9 α -hydroxyparthenolide ($\Delta E_{\text{gap}1} = 4.427$ eV) is smaller than the energy gap between HOMO of the 9 α -hydroxyparthenolide and LUMO of the morpholine ($\Delta E_{\text{gap}1'} = 6.699$ eV). This confirms that the global electron density transfer will go from the morpholine towards the 9 α -hydroxyparthenolide. But in the reaction (2), ΔE_{gap} between HOMO of the 9 α -hydroxyparthenolide and LUMO of the m-CPBA ($\Delta E_{\text{gap}2} = 4.522$ eV) is smaller than the energy gap between HOMO of the m-CPBA and LUMO of the 9 α -hydroxyparthenolide ($\Delta E_{\text{gap}2}' = 5.516$ eV) indicating that the GEDT will go from the 9 α -hydroxyparthenolide towards the m-CPBA (Figure 1).

Table 1. Electronic chemical potential μ , chemical hardness η , electrophilicity ω , nucleophilicity N and softness S calculated using B3LYP/6-311+G(d,p) (eV).

	Reaction 1 (In DCM)		Reaction 2 (In Ethanol)	
	9 α -hydroxyparthenolide	Morpholine	9 α -hydroxyparthenolide	m-CPBA
μ	-4.239	-3.103	-4.246	-4.748
η	4.754	6.372	4.799	5.238
ω	1.890	0.755	1.878	2.147
N	2.524	2.851	2.495	1.779
S	0.105	0.078	0.104	0.095
ΔN_{\max}	0.891	0.486	0.884	0.905

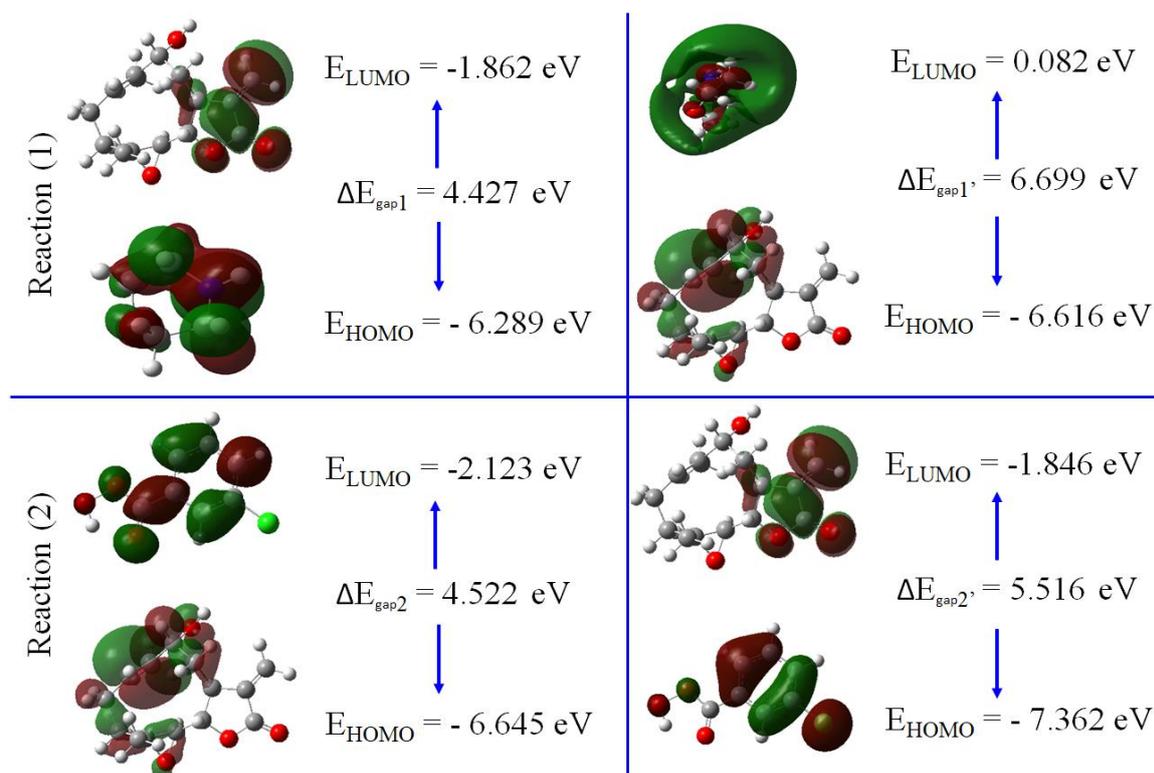


Figure 1. Energy gap between HOMO and LUMO of reagents in path reactions

3.1.2. prediction of the regio and stereoselectivity of the reactions

In the reactions involving the participation of non-symmetric reagents, the most favorable reactive channel was associated with the initial two-center interaction between the greatest electrophilic center of the electrophile unit and the greatest nucleophilic one of the nucleophile entities. Recently, Domingo et al.¹¹ proposed the electrophilic P_k^+ and nucleophilic P_k^- Parr functions derived from the changes of spin electron-density reached via the GEDT process from the nucleophile to the electrophile as a powerful tool

for the study of the local reactivity in polar processes. Accordingly, the nucleophilic P_k^- Parr functions of morpholine and the electrophilic P_k^+ Parr functions of the compound (II) were analyzed in order to characterize the most electrophilic and nucleophilic centers of the species involved in this reaction and, thus, to explain the regioselectivity experimentally observed. Figure 2 shows the Mulliken atomic spin densities of the radical cation and radical anion, together with the nucleophilic P_k^- Parr functions of morpholine and the electrophilic P_k^+ Parr functions of (II).

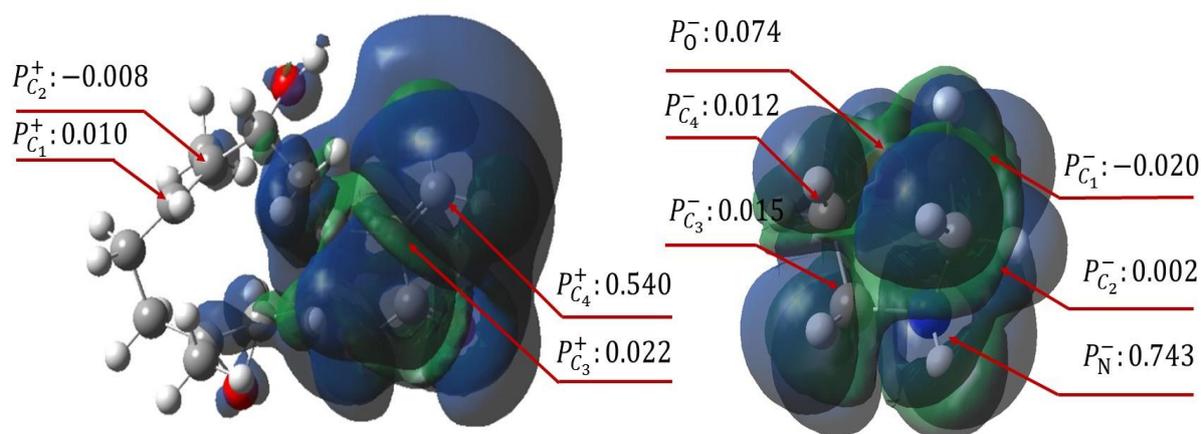


Figure 2. Three-dimensional representations of the Mulliken atomic spin densities (ASD) of the radical anion (II) and radical cation (Morpholine), together with the nucleophilic P_k^- of morpholine and electrophilic P_k^+ Parr functions of (II)

Analysis of the nucleophilic P_k^- Parr functions at the reactive sites of morpholine indicate that the azote atom, with a P_k^- value of 0.743 is nucleophilically activated more than the other atoms. On the other hand, the electrophilic P_k^+ Parr functions at the reactive sites of 9 α -hydroxyparthenolide indicate that the more electrophilic center is the C₄ carbon atom, which possessed the maximum value of 0.540 followed by the C₃ carbon atom, with a P_k^+ value of 0.022. These results indicate that the most reactive fragment of 9 α -hydroxyparthenolide is the C₃-C₄ double bond than the other double bond C₁-C₂. While in the second reaction, the analysis of the nucleophilic P_k^- Parr functions for 9 α -hydroxyparthenolide indicates that the two carbons of the C₁-C₂ double bond are more

nucleophilically activated ($P_k^- = 0.318$ and 0.466) than those of the C₃-C₄ double bond ($P_k^- = -0.021$ and 0.005) as shown in Figure 3. Consequently, the attack will take place on C₁-C₂ double bond rather than C₃-C₄ double bond of the 9 α -hydroxyparthenolide. The asymmetric nucleophilic activation of the exocyclic double bond accounts for the asynchronicity found in the formation of the two C-O single bonds in these epoxidation reactions. Therefore, it is expected that the attack of m-CPBA takes place on the C₁-C₂ double bond of 9 α -hydroxyparthenolide, in excellent agreement with experimental outcomes². Analysis of the electrophilic P_k^+ Parr functions for m-CPBA indicates that the oxygen atom O* is the most electrophilic center of this molecule ($P_k^+ = 0.018$).

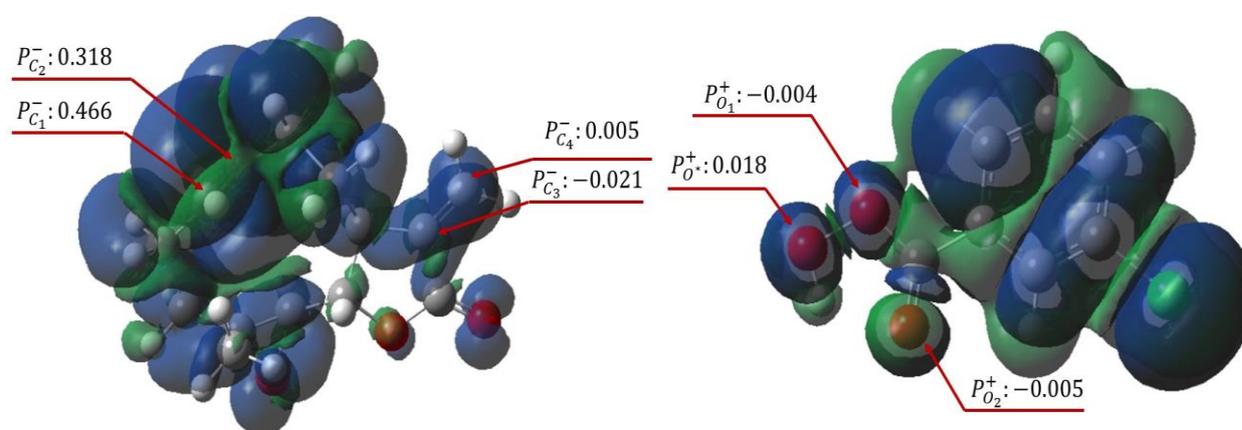


Figure 3. Three-dimensional representations of the (ASD) of the reagents (II) and m-CPBA, together with the nucleophilic P_k^- of (II) and electrophilic P_k^+ Parr functions of m-CPBA

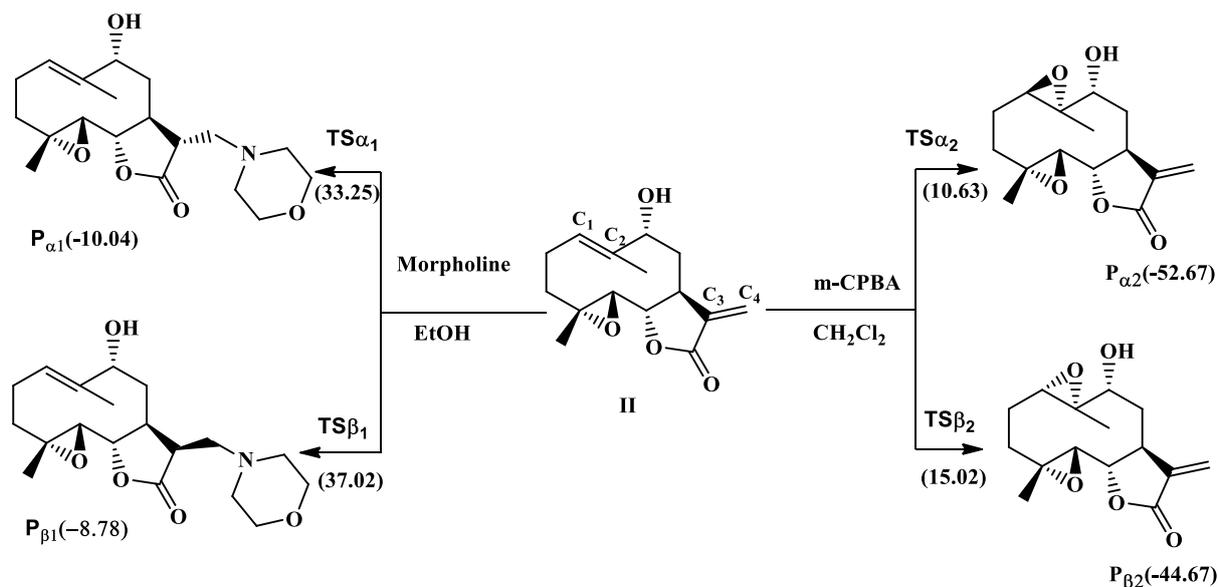
3.1.3. Analysis of the potential energy surface and prediction of the reaction mechanism

Due to the asymmetry of the reagents, two competitive channels are feasible for the reaction between 9 α -hydroxyparthenolide and morpholine. They are related to the two stereoisomeric approach modes of C₃-C₄ double bond, named endo $P_{\alpha 1}$ and exo $P_{\beta 1}$ as shown in Scheme 3. At the same time, the epoxy reaction of the 9 α -hydroxyparthenolide with the m-CPBA leads to a regio-stereoselective reaction with two products $P_{\alpha 2}$ and $P_{\beta 2}$ in C₁-C₂ double bond (Scheme 3).

In ethanol, the activation energies associated with the reaction between the 9 α -hydroxyparthenolide and the morpholine has occurred on the two faces of C₃-C₄ double bond. This reaction possesses activation energy of 33.25 kcal/mol via $TS_{\alpha 1}$, leading to the formation of the most favorable, $P_{\alpha 1}$, and 37.02 kcal/mol passing by $TS_{\beta 1}$, leading to the formation of the least favorable, $P_{\beta 1}$. In dichloromethane, the epoxidation of 9 α -hydroxyparthenolide by the m-CPBA presents activation energy of

10.63 kcal/mol via $TS_{\alpha 2}$, with the formation the most favorable, $P_{\alpha 2}$, and 15.02 kcal/mol via $TS_{\beta 2}$, with the formation the least favorable, $P_{\beta 2}$. These results of energies calculated by CDFT of transition states indicated that the two reactions proceed through a concerted pathway, and were in agreement with the experimentally observed regio and stereoselectivity².

An analysis of the stationary points involved in the two stereoisomeric paths indicates that these reactions take place through a one-step mechanism. Consequently, four transition states ($TS_{\alpha 1}$, $TS_{\beta 1}$, $TS_{\alpha 2}$, and $TS_{\beta 2}$) were located and characterized by the potential energy surface (PES) of these reactions. Relative enthalpies, ΔH , and Gibbs free energies, ΔG , for the species involved in the reaction between the 9 α -hydroxyparthenolide and the morpholine in the presence of ethanol and the reaction between the 9 α -hydroxyparthenolide and the m-CPBA in the presence of dichloromethane are displayed in Table 2.



Scheme 3. Reaction between (II) and morpholine (1), (II) and m-CPBA (2), B3LYP/6-311+G (d,p) relative energies, in kcal/mol, are given in parentheses

Table 2. B3LYP/6-311+G(d,p) relative enthalpies and Gibbs free energies, computed at room temperature and 1 atm for the stationary points involved in the reaction between morpholine, m-CPBA and (II).

	System	G (a.u)	H (a.u)	ΔG (Kcal/mol)	ΔH (Kcal/mol)	ν (cm ⁻¹)
Reaction 1	II	-884.441	-884.376	-	-	
	Morpholine	-287.771	-287.735	-	-	
	TS _{α1}	-1172.140	-1172.061	45.18	31.37	-1768.97
	TS _{β1}	-1172.134	-1172.054	48.94	35.76	-1740.68
	P _{α1}	-1172.225	-1172.131	-8.15	-12.55	
	P _{β1}	-1172.222	-1172.122	-6.27	-6.90	
Reaction 2	II	-884.439	-884.440	-	-	
	m-CPBA	-955.649	-955.602	-	-	
	TS _{α2}	-1840.060	-1840.030	17.57	7.53	-371.67
	TS _{β2}	-1840.020	-1840.011	42.67	19.45	-359.20
	P _{α2}	-959.662	-959.597	-49.57	-10.04	
	P _{β2}	-959.649	-959.584	-41.41	-1.88	

Some appealing conclusions can be drawn from the energy results relative to the enthalpies and Gibbs free energies of the stationary points and the transition states for the two reactions:

- The enthalpy energy associated with the most favorable product performed by the reaction of the 9 α -hydroxyparthenolide and the morpholine shows that TS_{α1} is located 4.39 kcal/mol below TS_{β1}.
- The Gibbs free energy associated with the most adequate (P_{α1}) reaction channel was -8.15 kcal/mol. This value shows that the reaction between 9 α -hydroxyparthenolide and morpholine is energetically exergonic.

For the epoxy reaction, the calculation of the energies of the reactants, the products obtained (TS_{α2} and TS_{β2}), transition states energies at the C₁=C₂ double bond of 9 α -hydroxyparthenolide and the difference in transition energy show that the attack is kinetically preferred at α side. This result shows that:

- The activation energies corresponding to the attack at the two sides of the C₁=C₂ double bond of 9 α -hydroxyparthenolide are 17.57 kcal/mol at α side and 42.67 kcal/mol at β side, suggesting that the formation of α isomers is kinetically preferred compared to the formation of β isomers;
- The formation of P_{α2} and P_{β2} is an exergonic reaction, with -49.57 and -41.41 kcal/mol, respectively.

We also notice that the energy barrier corresponding to the approach to the α -side in the two reactions is less than that corresponding to the β -side (Figure 4). This result allows us to conclude that the α -attack is

kinetically and thermodynamically favored. It also explains the great stereoselectivity observed experimentally².

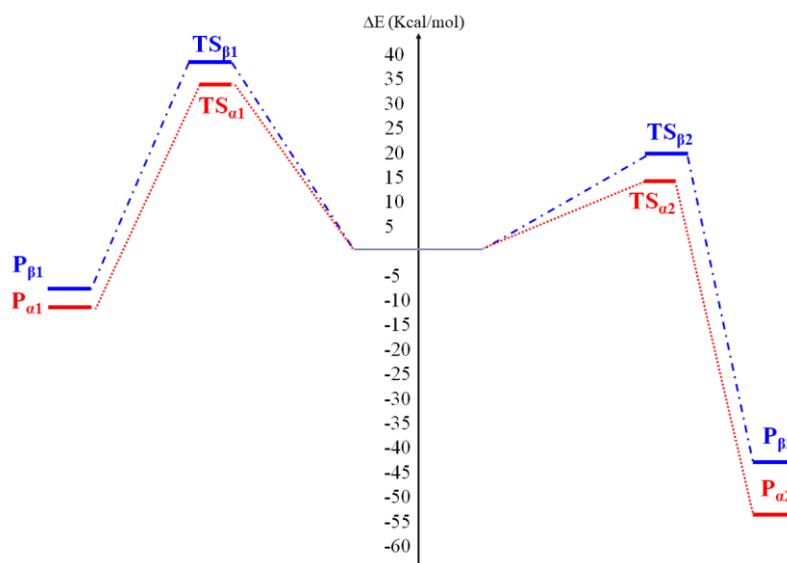


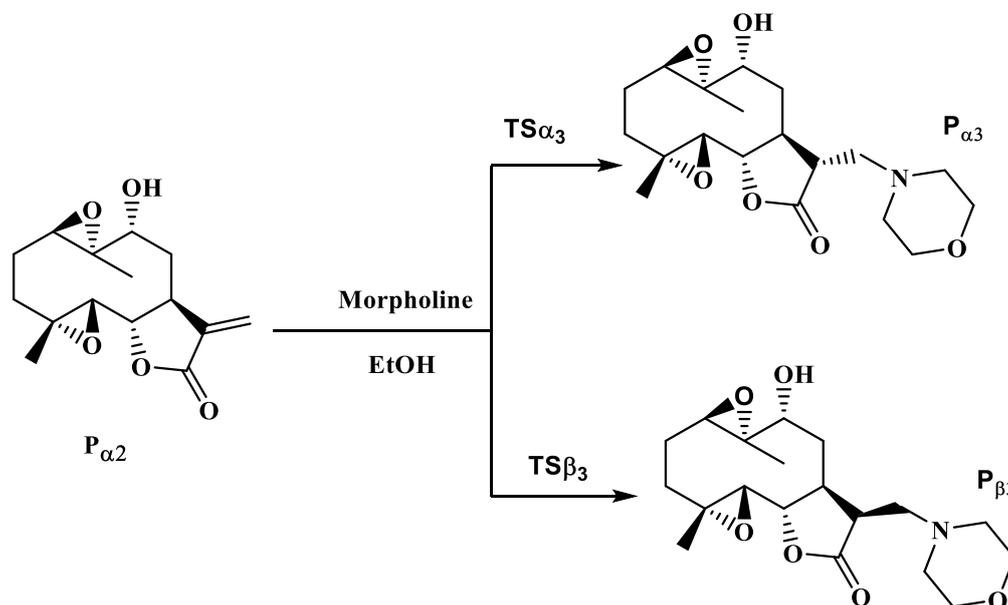
Figure 4. Energy profile of reactions between morpholine, m-CPBA, and 9 α -hydroxyparthenolide

3.2. Addition of morpholine onto major product

$P_{\alpha 2}$

The epoxidation reaction of 9 α -hydroxyparthenolide by m-CPBA was followed

by the addition of morpholine to the major product of the reaction ($P_{\alpha 2}$). The attack was carried out on the remaining C₃-C₄ double bond with two possible products $P_{\alpha 3}$ and $P_{\beta 3}$ (Scheme 4).



Scheme 4. Addition reaction of morpholine onto $P_{\alpha 2}$ product

3.2.1. Analysis of intramolecular chemical descriptors of the reaction between $P_{\alpha 2}$ and morpholine

To predict the reactivity of reagents in the reaction between morpholine and the major product, $P_{\alpha 2}$, founded as from the epoxy reaction of (II), we used B3LYP/6-311+G(d,p) level to calculate the global reactivity indices. Table 3 summarizes the obtained values of energy of HOMO and LUMO, the difference between $\epsilon(\text{HOMO})$ and $\epsilon(\text{LUMO})$ ΔE_{gap} ,

electronic chemical potential μ , chemical hardness η , global electrophilicity ω , nucleophilicity N and softness S of $P_{\alpha 2}$ and morpholine.

The big difference between $P_{\alpha 2}$ and morpholine in electronic chemical potential 1.65 eV, indicating that this reaction has an important polar character. The morpholine behaves as a nucleophile with an electrophilicity ω index of 0.755 eV and a nucleophilicity N index of 2.851 eV. In comparison,

$P_{\alpha 2}$ is classified as strong electrophile by ω index of 1.975 eV and a nucleophilicity N index of 1.527 eV.

To confirm the electrophilic/nucleophilic character of reagents, we have calculated the energy gap between HOMO and LUMO of the reactive molecules in this reaction. ΔE_{gap} between HOMO of

$P_{\alpha 2}$ and LUMO of morpholine, $\Delta E_{\text{gap}} = 6.531$ eV is higher than the energy gap between HOMO of morpholine and LUMO of $P_{\alpha 2}$, $\Delta E_{\text{gap}}' = 4.396$ eV. This result confirms that the GEDT will go from the morpholine towards $P_{\alpha 2}$.

Table 3. Intramolecular chemical descriptors (eV) for $P_{\alpha 2}$ and morpholine, taking the HOMO energy of tetracyanoethylene (TCE) as a reference [ϵ_{HOMO} (TCE) = - 0.3359 (a.u) = -9.1413 (eV)].

	$P_{\alpha 2}$		Morpholine	
$\epsilon(\text{HOMO})$	-7.613	$\Delta E_{\text{gap}} = 6.531$	-6.289	$\Delta E_{\text{gap}}' = 4.396$
$\epsilon(\text{LUMO})$	-1.893		-0.082	
μ	-4.753		-3.103	
η	5.719		6.372	
ω	1.975		0.755	
N	1.527		2.851	
S	0.087		0.078	
ΔN_{max}	0.831		0.486	

3.2.2 Kinetic and thermodynamic study

The stereoselectivity of the addition of morpholine to the major product obtained from the epoxidation reaction of 9 α -hydroxypartenolide ($P_{\alpha 2}$) has been examined for both α and β sides. Calculated energies using the DFT method for the reagents, the obtained products ($\text{TS}_{\alpha 3}$ and $\text{TS}_{\beta 3}$), and the difference in transition energy are listed in Table 4.

From Table 4 we can deduce that:

- The transition state energy of the β side of double bond $\text{C}_3=\text{C}_4$ is located in front of 32.80 and 30.34 kcal/mol above the transition state energy of the α side respectively;

- The formation of products $P_{\alpha 3}$ and $P_{\beta 3}$ are an exothermic reaction by -16.16 and -10.13 kcal/mol, respectively.

We can also notice that the energy barrier corresponding to the approach of the α -side is less than that corresponding to the β -side. These results allow us to conclude that α -attack is kinetically and thermodynamically favored.

Therefore, these energy results calculated by CDFT of the transition states showed that the reaction proceeds through a concerted pathway, in agreement with the experimentally observed regio and stereoselectivity in previous studies by our co-authors².

Table 4. Thermodynamic energies of the reaction between $P_{\alpha 2}$ and morpholine calculated using B3LYP/6-311+G (d,p) basis set.

	E (a.u)	G (a.u)	H (a.u)	$\Delta E(\text{Kcal/mol})$	$\Delta G(\text{Kcal/mol})$	$\Delta H(\text{Kcal/mol})$
$P_{\alpha 2}$	-959.953	-959.665	-959.600			
Morpholine	-287.876	-287.771	-287.735			
$\text{TS}_{\alpha 3}$	-1247.780	-124.365	-1247.285	30.34	44.55	31.37
$\text{TS}_{\beta 3}$	-1247.777	-1247.369	-1247.289	32.80	42.04	28.86
$P_{\alpha 3}$	-1247.855	-1247.438	-1247.358	-16.16	-1.25	-14.43
$P_{\beta 3}$	-1247.845	-1247.429	-1247.348	-10.13	4.39	-8.15

3.2.3. Analysis of the IRC of the reaction between $P_{\alpha 2}$ and morpholine

The cycloaddition reaction may have one of the two main mechanisms, concerted or stepwise. The concerted mechanism involves a single step with the asynchronous formation of two bonds, or a single step with two phases, characterized by the formation of the first bond followed by the closure of the cycle

without the formation of a stable intermediary reactant, while the two-step mechanism involves an intermediary reactant. Moreover, we studied the molecular system as it develops during the reaction between $P_{\alpha 2}$ and morpholine by calculating the intrinsic reaction coordinate (IRC) to show that the transition state is indeed linked to the two minima (reactants and product).

The plots $E=f(\text{IRC})$ corresponding to all possible pathways are shown in Figure 5. IRC calculation shows that this reaction follows a concerted mechanism in a single step but two phases. Analysis of the IRC calculated using B3LYP/6-311+G(d,p)

basis set shows that whatever quantity of morpholine is used in the interaction with $P_{\alpha 2}$, the transition states are reached without going through a stable intermediary stage.

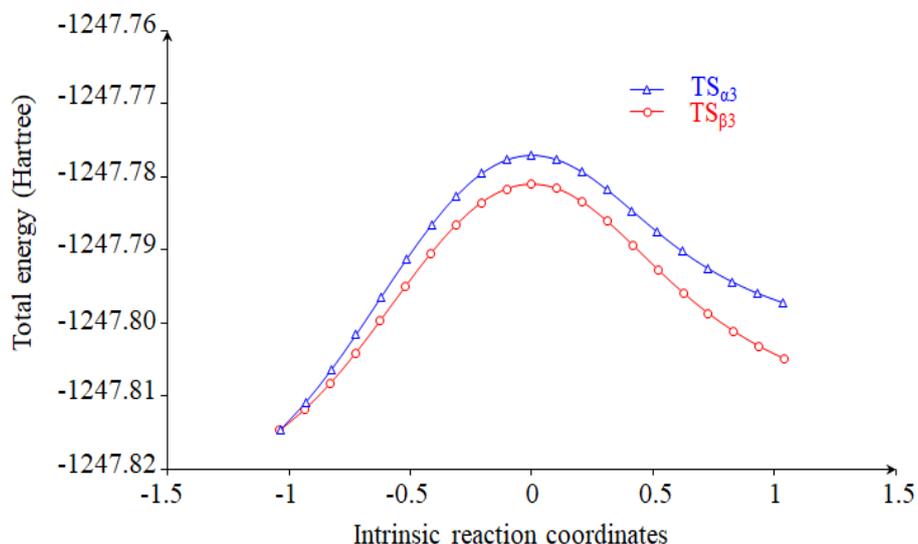


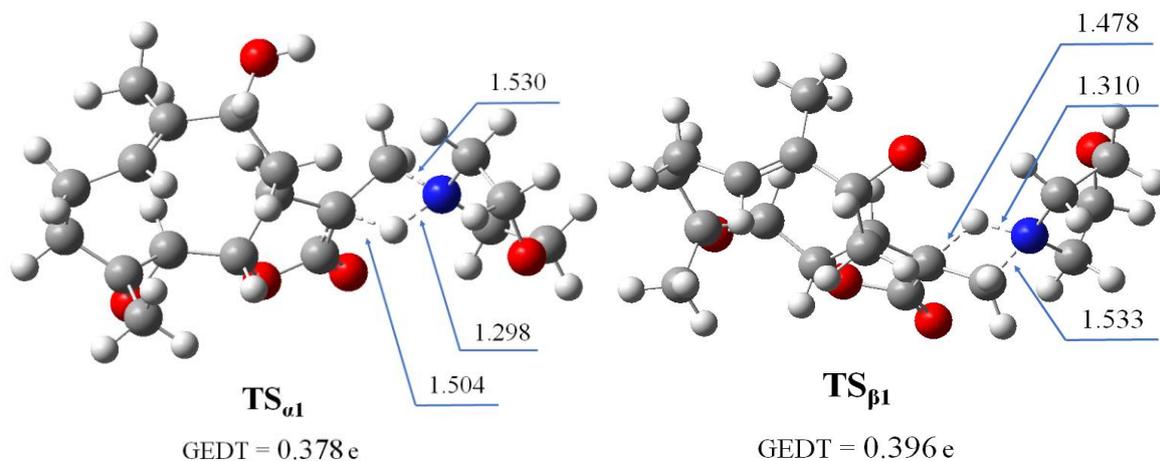
Figure 5. IRC profiles of the reaction between $P_{\alpha 2}$ and morpholine calculated using B3LYP/6-311+G (d,p) level

3.3. Structural analysis of the transition states of all reactions

The geometries of the TS associated with the reaction between $P_{\alpha 2}$ and morpholine are shown in Figure 6. The lengths of the two forming bonds at the TS associated with the reaction between the 9α -hydroxyparthenolide in each reaction are different, indicate that they are associated with slightly asynchronous.

To evaluate the polar nature of the all studied reaction. The GEDT values computed at the TS of

the reaction between the 9α -hydroxyparthenolide and morpholine are: 0.378e at $\text{TS}_{\alpha 1}$ and 0.396e at $\text{TS}_{\beta 1}$, and TS of the reaction of 9α -hydroxyparthenolide with m-CPBA are: 0.580e and 0.593e at $\text{TS}_{\alpha 2}$ and $\text{TS}_{\beta 1}$, respectively. While, for the TS of the reaction between $P_{\alpha 2}$ and morpholine are: 0.342e and 0.368e at $\text{TS}_{\alpha 3}$ and $\text{TS}_{\beta 3}$, respectively. These very high values indicate the polar character of these reactions, in a perfect agreement with the analysis of the CDFT reactivity indices of the reagents.



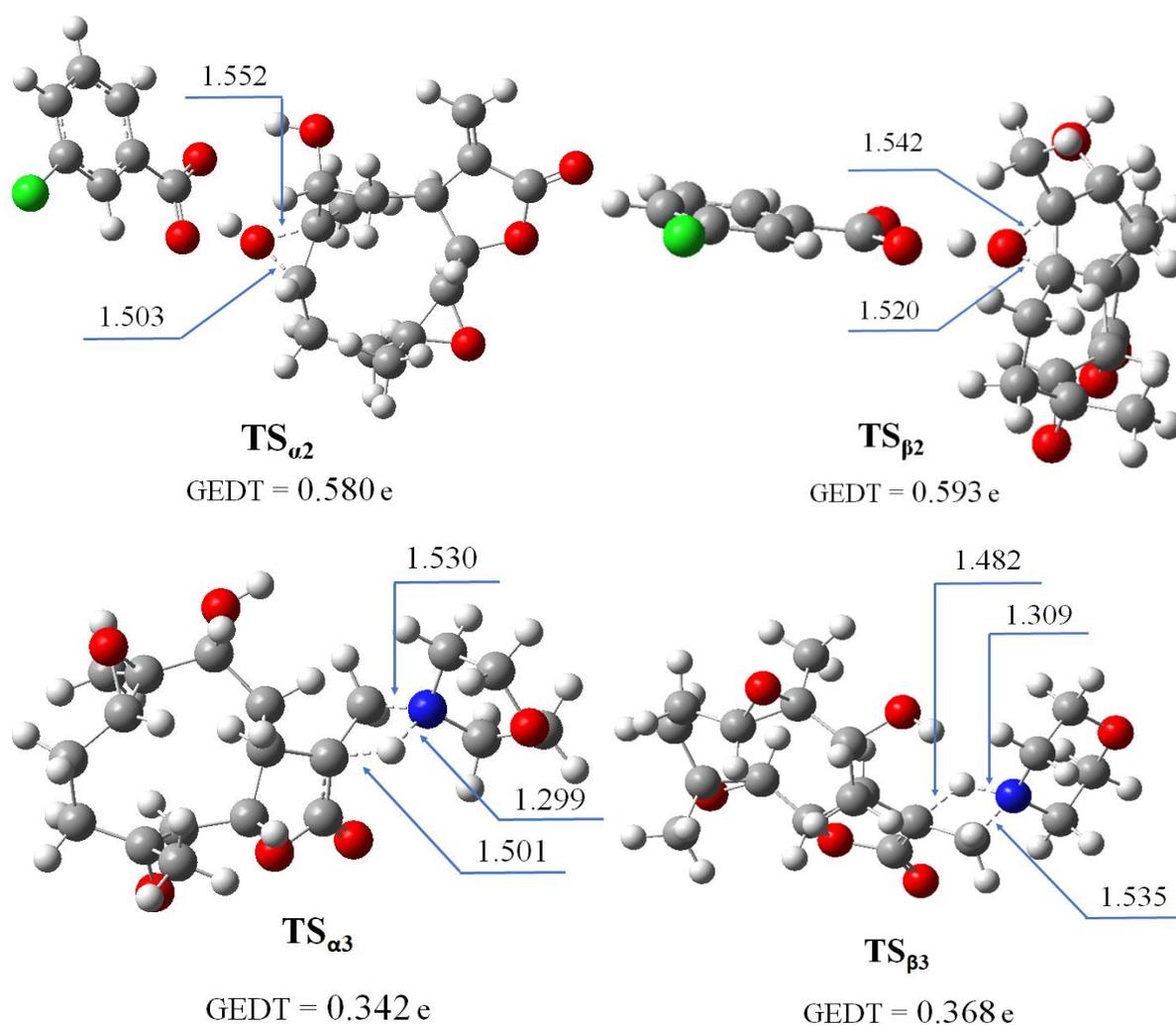


Figure 6. Geometries and lengths of the forming bonds, in Angstroms, and GEDT values, in e, of the TS involved in all reactions

4. Conclusion

The mechanism of the chemo- and the stereoselectivity for the addition of morpholine and m-CPBA onto 9 α -hydroxyparthenolide was studied using B3LYP/6-311+G (d, p). The theoretical results obtained enabled us to conclude that the activation energies and reactivity indices calculated correctly predicted the chemoselectivity experimentally observed for the studied reactions. In the first step, the reaction between the morpholine and the 9 α -hydroxyparthenolide takes place on the double bond C₃=C₄ giving two products P_{α1} and P_{β1}, with P_{α1} as the major product according to kinetic and thermodynamic calculations. On the other hand, when 9 α -hydroxyparthenolide is attacked by m-CPBA, the epoxidation reaction is carried out on the double bond C₁=C₂ of the compound (II), producing a minority of the β -stereoisomer, referred as P_{β2} and a majority of the α -stereoisomer, referred to here as P_{α2}. This latter was thereafter treated with morpholine via an exothermic reaction leading to the formation of the two products P_{α3} and P_{β3} who are formed at the α and β sides, respectively, of the C₃=C₄ double bond of P_{α2}. The product P_{α3} is

kinetically and thermodynamically favored with high stereoselectivity.

The results we found do affirm that the density functional theory has given a conceptual framework to the study of the reactivity and selectivity of a chemical reaction through local and global descriptors and the polar character of these reactions is correlated with the course of the corresponding GEDT to TS in such a way that the higher the GEDT implies that the activation energy is low and the reaction is polar.

References

- 1- A. Ghantous, A. Sinjab, Z. Herceg, N. Darwiche, Parthenolide: from plant shoots to cancer roots, *Drug discovery today*, **2013**, 18, 894–905.
- 2- M. Moumou, A. R. El Bouakher, H. Allouchi, A. El Hakmaoui, A. Benharref, V. Mathieu, G. Guillaumet, M. Akssira, Synthesis and biological evaluation of 9 α - and 9 β -hydroxyaminoparthenolides as novel anticancer agents, *Bioorg. Med. Chem. Lett.*, **2014**, 24, 4014-4018.

- 3- H. Eyring, the energy of activation for bimolecular reactions involving hydrogen and the halogens, according to the quantum mechanics, *J. Am. Chem. Soc.*, **1931**, 53, 2537-2549.
- 4- K. Fukui, T. Yonezawa, H. Shingu, A molecular orbital theory of reactivity in aromatic hydrocarbons, *J. Chem. Phys.*, **1952**, 20, 722-725.
- 5- G. Klopman, Chemical reactivity and the concept of charge-and frontier-controlled reactions, *J. Am. Chem. Soc.*, **1968**, 90, 223-234.
- 6- R. G. Parr, R. G. Pearson, Absolute Hardness: Companion Parameter to Absolute Electronegativity, *J. Am. Chem. Soc.*, **1983**, 105, 7512-7516.
- 7- S. El Hamidi, M. Khnifira, A. Elhalil, R. Hammal, N. Barka, M. Sadiq, A. Benharref, H. Lafridi, H. Zgou, M. Abdennouri, A theoretical study of regio and stereoselectivity nitration of thymol and carvacrol using DFT approach, *Mor. J. Chem.*, **2019**, 7, 363-372.
- 8- L. R. Domingo, M. R. Gutiérrez, P. Pérez, A new model for C-C bond formation processes derived from the Molecular Electron-Density Theory in the study of the mechanism of [3+2] cycloaddition reactions of carbenoid nitrile ylides with electron-deficient ethylenes, *Tetrahedron*, **2016**, 72, 1524-1532.
- 9- R.G. Parr, L.V. Szentpaly, S. Liu, Electrophilicity index, *J. Am. Chem. Soc.*, **1999**, 121, 1922-1924.
- 10- R. Hammal, M. Zoubir, A. Benharref, A. El Hajbi, Natural Bond Orbital Population Analysis of α -trans-himachalene, *Research Journal of Pharmaceutical Biological and Chemical Sciences*, **2017**, 8(6), 423-432.
- 11- L. R. Domingo, P. Pérez, The nucleophilicity N index in organic chemistry, *J. Org. Biomol. Chem.*, **2011**, 9, 7168-7175.
- 12- L. R. Domingo, P. Pérez, J. A. Sáez, Understanding the local reactivity in polar organic reactions through electrophilic and nucleophilic Parr functions, *RSC Advances*, **2013**, 3, 1486-1494.
- 13- A. Zeroual, R. Hammal, A. Benharref, A. El Hajbi, The regio- and stereoselective addition of dibromocarbene and dichlorocarbene onto β -himachalene, *Mor. J. Chem.*, **2015**, 3, 698-704.
- 14- W. Yang, W.J. Mortier, The Use of Global and Local Molecular Parameters for the Analysis of the Gas-Phase Basicity of Amines, *J. Am. Chem. Soc.*, **1986**, 108, 5708-5711.
- 15- R. K. Otmane, T. S. Ouk, R. Bahadi, A. Bouzina, S.D. Djouad, K. Bechlem, R. Zerrouki, T. Ben Hadda, F. Almalki, M. Berredjem, Synthesis, DFT and POM analyses of cytotoxicity activity of α -amidophosphonates derivatives: Identification of potential antiviral O, O-pharmacophore site, *J. Mol. Struct.*, **2019**, 1197, 196-203.
- 16- P. Pérez., L. R. Domingo, M. Duque-Noreña., E. A. Chamorro, A condensed-to-atom nucleophilicity index. An application to the director effects on the electrophilic aromatic substitutions, *J. Mol. Struct.Theochem.*, **2009**, 895, 86-91.
- 17- H. B. Schlegel, Optimization of equilibrium geometries and transition structure, *J. Comput. Chem.*, **1982**, 3, 214-218.
- 18- R. Hammal, A. Benharref, A. El Hajbi, Exploitation of the mechanism and selectivity of [1+2] cycloaddition reaction between α - cis-himachalène and dibromocarbène using DFT-based reactivity indices, *J. CMMDA*, **2015**, 5, 16-24.
- 19- W. J. Hehre, L. Radom, P. R. Schleyer, Ab Initio Molecular Orbital Theory, *Journal of Computational Chemistry*, **1986**, 7, 379-383.
- 20- H. B. Schlegel, Geometry optimization on potential energy surfaces, *Modern Electronic Structure Theory: Part I*, **1995**, 459-500.
- 21- M. J. Frischet, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, Gaussian 09, Gaussian Inc., Wallingford CT, **2009**.